UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/698,034	10/30/2003	Jean-Claude Yvin	16721-0260 (42528-294219)	1182

23370 7590 08/25/2004

JOHN S. PRATT, ESQ
KILPATRICK STOCKTON, LLP
1100 PEACHTREE STREET
ATLANTA, GA 30309

EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 08/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/698,034	YVIN ET AL.	
	Examiner	Art Unit	
	Brandon J Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) *1-9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Specification

The disclosure is objected to because of the following informalities: The specification does not provide a reference to and brief description of the drawing(s) as set forth in 37 CFR 1.74..

Appropriate correction is required.

Claim Objections

Claim 9 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 9 is a dependent claim upon claim 9.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3 and 5-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 3 is rejected as vague and indefinite for reciting "molecular determinants" in claim 3. The term "molecular determinant" is not defined by the claim, and the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Regarding claims 1 and 5-8, the phrase "like" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Regarding claims 2 and 8, the phrase "preferably" renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating cancer comprising administering intraperitoneally of a composition comprising a monoclonal antibody with Laminarin (500 mg/kg, once a day for 5 days), does not reasonably provide enablement for treating cancer comprising administering a composition comprising a monoclonal antibody with all oligo-β-(1,3)-glucans presented in formula (1) at any dose and through any pathway. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining

whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The instant claims read on a method of treating cancer comprising administering a composition comprising a monoclonal antibody with either a β-(1,3)-glucan like laminarin or an oligo- β -(1,3)-glucan presented in formula (1) (claim 2) to a human or warm blooded animal, wherein the composition is administered intravenously or intraperitoneally either simultaneously, sequentially, or successively under the form of injection, ointment, pulmonary spray or orally, wherein the effective amount of the oligo- β -(1,3)-glucan is 2 o 20 mg/kg when administered orally.

The specification teaches (page 9, Example shown in Figure 1) a synergistic effect of a monoclonal antibody, specifically Herceptin, with Laminarin (Phycarine®) on tumor growth in-vivo in female nude mice implanted with human tumor carcinoma. The specification also teaches that the mice of each group were administered intraperitoneally with 2 mL of the composition. Further, the specification teaches (figure 1) test group 5, containing 500mg/kg Phycarine (laminarin) (once a day for 5 days) and 0.5mg/kg Herceptin (twice a week during 3 weeks), allowed a limitation in the increase of tumor weight compared to test group 4, 250mg/kg Phycarine (once a day for 5 days) and 0.5mg/kg Herceptin (twice a week during 3 weeks), which did not limit an increase in tumor weight. In addition, the specification is silent on the in-vivo efficacy of other compositions which include, but are not limited to, any and/or all oligo- β -(1,3)-glucans presented in formula (1) at any dose and through any pathway, specifically orally wherein the effective amount is 2 to 20mg/kg. Therefore, it would not be predictable that any dosage of Phycarine would limit an increase in tumor weight; only a dose of 500mg/kg Phycarine (laminarin) (once a day for 5 days).

One cannot extrapolate the teachings of the specification to the scope of the claims because the claims are broadly drawn to treating cancer with any and all compositions comprised of a monoclonal antibody and an oligo- β -(1,3)-glucan at any dose and through any pathway, and applicant has not enabled all of these compositions because it has not been shown that these compositions i.e. monoclonal antibody and all combinations of the oligo- β -(1,3)-glucans presented in formula (1) are capable of functioning as to that which is being disclosed.

For example, those of skill in the art would recognize the unpredictability of treating cancer with unsubstituted derivatives of oligo-(1-3)- β -glucans. For example, Bohn et al. (Carbohydrate Polymers, 28, 3-14, 1995) discloses a review of structure-functional activity relationships of (1-3)B-D-Glucans as biological modifiers. This includes the importance of the (1-3) linked β -glucan backbone to the expression of antitumor activity, and the influence of glycosyl units attached to O6 (page 6, 1st column, 1st paragraph). Specifically, that the (1-3)-linked backbone structure is essential, i.e. antitumor activity is absent when the polymer is unbranched (i.e. curdlan), but can be induced by branching with glucosyl units at the O6 position (page 6, 1st column, 1st paragraph). Thus, it appears that the antitumor activity would be absent from the linear, unbranched oligo-β-(1,3)-glucan polymer of formula 1. Therefore, one would not be able to predict its anticancer potential, nor would one of ordinary skill in the art be able to presume a synergistic relationship between the oligo-β -(1,3)-glucans presented in formula 1 and a monoclonal antibody for the treatment of cancer. Further, treatment of cancer in general is at most unpredictable, as underscored by Gura (Science, v278, 1997, pp.1041-1042) who discusses the potential shortcomings of potential anti-cancer agents including extrapolating from in-vitro to in-vivo protocols, the problems of drug testing in knockout mice, and problems associated with clonogenic assays. Indeed, since formal screening began in 1955, thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the FDA (page 1041, 1st column) wherein the fundamental problem in drug discovery for cancer is that the model systems are not predictive. All of this underscores the criticality of providing workable examples which is not disclosed in the specification, particularly in an unpredictable art such as cancer therapy.

In view of the teachings above and the lack of guidance, workable examples and or exemplification in the specification, it would require undue experimentation by one of skill in the art to determine with any predictability, that the method would function as broadly claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Cheung (WO 02/058711 A1, August 1, 2002).

Claims 1-8 are drawn to a method of treating cancer comprising administering a composition comprising a monoclonal antibody specific to molecular determinants present on cancer cells and simultaneously able to activate complement with either a β -(1,3)-glucan like laminarin or an oligo- β -(1,3)-glucan presented in formula (1) (claim 2) to a human or warm blooded animal, wherein the composition is administered intravenously or intraperitoneally either simultaneously, sequentially, or successively under the form of injection, ointment, pulmonary spray or orally, wherein the effective amount of the oligo- β -(1,3)-glucan is 2 to 20 mg/kg when administered orally.

Cheung teaches a method for treating a subject with cancer comprising administering a composition comprising an effective amount of glucan capable of enhancing the efficacy of antibodies, specifically, monoclonal antibodies against cancer (page 4, lines 22+). The reference also teaches (page 15, lines 10-11) that in a further embodiment, the antibody is capable of activating complement. Cheung further teaches the cancer recognized by antibodies includes but not limited to neuroblastoma, melanoma, non-hodgkin's lymphoma, ... leukemia, breast cancer, ovarian cancer, lung cancer, ... ect (page 4, lines 9+). With regard to the β-glucan, the reference teaches (page 8, line 30+, figure 6) a synergistic relationship was observed between laminarin (open squares, purchased from Sigma) and antibody 3F8.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cheung (WO 02/058711 A1, August 2002) as applied above to claims 1-8, and further in view of Tschmelitsch *et al.* (Canc. Res., 1997, Vol.57, No.11, abstract).

Cheung teaches as set forth above with regard to claims 1-8, a method for treating a subject with cancer comprising administering a composition comprising an effective amount of glucan capable of enhancing the efficacy of antibodies, specifically, monoclonal antibodies against cancer (page 4, lines 22+). The reference also teaches (page 15, lines 10-11) in a further embodiment, the antibody is capable of activating complement. Cheung further teaches the cancer recognized by antibodies includes but not limited to neuroblastoma, melanoma, non-hodgkin's lymphoma, ... leukemia, breast cancer, ovarian cancer, lung cancer, ... ect (page 4, lines 9+). With regard to the β-glucan, the reference teaches (page 8, line 30+, figure 6) a synergistic relationship was observed between laminarin (open squares, purchased from Sigma) and antibody 3F8.

Cheung does not teach that the composition comprising a monoclonal antibody with a oligo-β-(1,3)-glucan further comprises a chemotherapeutic agent.

Tschmelitsch *et al.* teaches (title) an enhanced antitumor activity of combination radio immunotherapy with chemotherapy (fluorouracil).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine a chemotherapeutic agent with a composition comprising an antibody. As evidenced by Tschmelitsch *et al*, it is well known in the art that chemotherapeutics, such as fluorouracil, when used in combination with specific antineoplastic antibodies, can enhance the anticancer effects versus the effects when either agent is used alone. Thus, one of ordinary skill

in the art would have a reasonable expectation that by combining chemotherapy with the compositions comprising a monoclonal antibody with a β-glucan used by Cheung, one would achieve enhanced antineoplastic effects.

Therefor, NO claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 8:30 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Brandon J Fetterolf, PhD
Examiner
Art Unit 1642

BF

GARY NICKOL
PRIMARY EXAMINER